

# Diagnostic discrepancy between bronchoalveolar lavage and transbronchial biopsy from bronchoscopies of HIV patients with pneumonia: toward an integral diagnosis

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**Background:** The key diagnostic method for the evaluation of lung diseases associated with HIV infection is bronchoscopy, with bronchoalveolar lavage (BAL) being the most commonly used sampling technique. Transbronchial biopsy (TBB) is often complementary.

**Setting:** This is a retrospective cross-sectional study to determine the diagnostic usefulness of bronchoscopy with simultaneous samples obtained through BAL and TBB in HIV-infected patients with pneumonia at the National Institute of Respiratory Diseases Ismael Cosío Villegas.

**Methods:** In this cross-sectional study (January 2014–December 2015), the diagnostic yield of bronchoscopic samples from all HIV-positive patients with pneumonia aged >18 years, from procedures performed in the Interventional Pulmonology Unit, was analyzed and recorded in its database. The diagnostic yield concordance between BAL and TBB samples was evaluated by kappa index calculation.

**Results:** A total of 198 procedures on 189 HIV-infected patients with pneumonia were performed. A total of 167/189 (88.4%) patients were male, and the mean age was 34.7 years (SD  $\pm 9.0$ ). Overall, the diagnostic yield for either technique was 87.9% (174/198), but it was higher for TBB, its yield being 78.8% (156/198). In contrast, that of BAL was 62.1% (123/198) ( $P=0.001$ ). The overall diagnostic yield concordance between TBB and BAL was insignificant ( $\kappa=0.213$ ,  $P<0.001$ ). It improved for fungal infections, pneumocystosis, and tuberculosis ( $\kappa=0.417$ , 0.583, and 0.462, respectively, all  $P<0.001$ ).

**Conclusion:** Our results show that the simultaneous obtainment of BAL and TBB samples is useful and complementary in the diagnosis of infections and malignancies in HIV-infected patients. Additionally, they are safe procedures in this group of patients.

**Keywords:** bronchoalveolar lavage, transbronchial biopsy, HIV, BAL, TBB, interventional bronchoscopy, bronchoscopy

## Background

Respiratory diseases are frequent in HIV-infected patients and are a leading cause of morbidity and mortality despite combined antiretroviral therapy (ART). The spectrum of pulmonary manifestations is wide and includes infectious and noninfectious diseases, which frequently have overlapping clinical and radiological manifestations. Additionally, coinfections are frequent and their isolation with conventional methods is difficult. The most frequent infections are bacterial pneumonia, tuberculosis, *Pneumocystis jirovecii* pneumonia (PJP), and fungal infections (coccidioidomycosis, histoplasmosis, and cryptococcosis).<sup>1–6</sup> The key diagnostic method for the evaluation of lung diseases

associated with HIV is bronchoscopy, with bronchoalveolar lavage (BAL) being the most commonly used sampling technique, while transbronchial biopsy (TBB) is often complementary. Both are useful and safe procedures.<sup>2,7</sup> However, the utility of each of these techniques in infectious diseases is different, especially for PJP and cytomegalovirus (CMV) infection, and TBB is more useful for bacterial infections and noninfectious disease such as malignancies.<sup>2,8</sup> Our objective was to determine the diagnostic usefulness of bronchoscopy with simultaneous sampling obtained with BAL and TBB in HIV-infected patients with pneumonia.

## Methods

This is a retrospective cross-sectional study, which was approved by the Research and Ethics Committees of the National Institute of Respiratory Diseases Ismael Cosío Villegas of Mexico, with code number C72-16. Informed consent waiver from the Institutional Research and Ethics Committees was requested, since this was a retrospective study, and the confidentiality of the patients included in the study was strictly protected. A total of 189 patients older than 18 years diagnosed with HIV and registered in the database of the Interventional Pulmonology Unit of our institution were subjected to a diagnostic bronchoscopy, which included BAL and TBB. The patients were admitted to the External Consultation Service, the Emergency Department and Clinical Services of the INER, or were referred by medical interconsultation from other institutions because they presented with pneumonia diagnosed either clinically or by chest tomography, with indication to perform diagnostic bronchoscopy by means of BAL and TBB study during the period from January 2014 to December 2015. The population size was 198 procedures, considering 1) the finite population correction factor ( $N$ ), an estimated 400 outpatients or hospitalized patients with HIV and pneumonia treated within 2 years at the institute; 2) an overall diagnostic yield of 50% ( $\pm 5$ ), according to the published variability of the diagnostic yields of the different pulmonary samples; 3) 95% CIs; and 4) the formula:  $N = (EDFF \times Np [1 - p]) / (d^2 / Z^2 - \alpha/2 \times [N - 1] + p \times [1 - p])$ , which was obtained through the OpenEpi software, Version 3.

BAL and TBB samples were cultured as follows. In fungal infection, the samples were cultured on sabouraud and sabouraud with antibiotics culture media and the species were identified under the cotton blue microscopy. For the diagnosis of *P. jirovecii*, direct immunofluorescence microscopy, as the gold standard, was performed. Special staining with grocott, calcofluor white, and Wright stains for fungal identification was also performed. In mycobacteria, the samples were

cultured on liquid (BACTEC MGIT 960) and solid (Löwenstein–Jensen) media and the species were identified using the line probe assay (HAIN) tests. For drug susceptibility testing in *Mycobacterium tuberculosis*, BACTEC MGIT 960 SIRE kit was used. GeneXpert® MTB/RIF for *M. tuberculosis* diagnosis was also performed in all samples. In bacteria, the samples were cultured on liquid and solid agar media and automated VITEK 2 was used for identification and drug susceptibility testing. In viral infection, multiplex real-time polymerase chain reaction (PCR) LUMINEX assay for respiratory viral diagnosis and Anyplex™ II multiplex real-time PCR RPB5 for respiratory bacteria platforms were performed. In CMV, tissue real-time PCR and histopathological analysis were performed.

Samples for histopathological analysis obtained transbronchially (TBB) were kept in formaldehyde buffer, pH 7.1 (EMD Millipore, Billerica, MA, USA), and BAL samples were kept in 10 cc carbowax (polyethyleneglycol 4000; Merck Millipore, Billerica, MA, USA).

All procedures were performed and supervised by an expert interventional pulmonologist.

BAL is performed using the pulmonary bronchoscopic wedging technique in the most affected lung subsegment with 180 mL saline instillation, recovering at least 45% of instillate. The material collected in vial-like containers is sent to the Microbiology and Anatomic Pathology Department.

In TBB, lung biopsy is performed using the bronchoscopic wedging technique at the most affected site under fluoroscopic guidance and is sent to the Microbiology and Anatomic Pathology Department.

Helical computed tomography of the chest with contrast was performed, with reconstruction in window for the lung and mediastinum, with a section thickness of 3 mm with SIEMENS SOMATOM tomograph definition 128. Prior to tomography, the site with the greatest damage is identified, and TBB and BAL are performed.

Variables were evaluated according to their distribution. The diagnostic yield of the samples obtained by bronchoscopy (BAL and TBB) was analyzed with chi-square and Fisher's exact tests for categorical variables, and *t*-test was used for continuous independent variables. The kappa index was used to evaluate the diagnostic yield concordance between the samples obtained with BAL and TBB. Results were significant at a *P*-value of <0.05. The statistical analysis was performed using the IBM SPSS Statistics 21 software.

## Results

A total of 198 procedures on 189 HIV-infected patients with pneumonia were performed. A total of 167/189 (88.4%)

patients were male, with a mean age of 34.7 years (SD  $\pm 9.0$ ) (Table 1). Information about previous ART or antibiotic therapy prior to bronchoscopy was available from 167 patients (84.3%). A total of 92.8% (155/167) of patients had taken antibiotics for a mean of 5.4 days (SD  $\pm 5.8$ ), and 36.6% (60/164) of patients were on ART prior to evaluation, with a mean ART duration of 7.3 months (SD  $\pm 22.6$ ) prior to bronchoscopy.

## Overall diagnostic yield

Overall diagnostic yield for either technique was 87.9% (174/198), but it was higher for TBB, the yield of this method being 78.8% (156/198) in contrast to 62.1% (123/198) for BAL ( $P=0.001$ ). The most frequent diagnosis was infections, with etiologic agent identification in 79.3% (157/198) (Tables 1 and 2).

**Table 1** Summary of procedures performed on 189 HIV-infected patients with pneumonia subjected to 198 bronchoscopies

Patients' characteristics	n	%
Males	167	88.4
Mean age $\pm$ SD	34.7	9.0
Type of samples and processing		
BAL samples	198	100.0
BAL samples processed in Pathological Anatomy	191	96.5
BAL samples subjected to microbiological processing	198	100.0
TBB samples	198	100.0
TBB samples processed in Pathological Anatomy	193	97.5
TBB samples subjected to microbiological processing	192	97.0
Absolute CD4 <sup>+</sup> cell counts		
<50/mm <sup>3</sup>	106	57.0
50–99/mm <sup>3</sup>	32	17.2
100–199/mm <sup>3</sup>	21	11.3
200–499/mm <sup>3</sup>	19	10.2
$\geq 500$ /mm <sup>3</sup>	8	4.3
Population with known history of antibiotic use prior to bronchoscopy	155/167	92.8
Population with known history of antiretroviral treatment took prior to bronchoscopy	60/164	36.6
Global diagnosis		
Infectious agent	157/198	79.3
With a single etiologic agent*	102/157	64.9
With more than a single agent (coinfections)	55/157	35.0
Noninfectious, benign	14/198	7.0
Malignancy	3/198	3.0
Mixed (malignancy with etiologic agent)	3/198	3.0
Global diagnostic yield of bronchoscopy	174/198	87.9
Without diagnosis from bronchoscopy	24/198	12.1

Note: \*TBB.

Abbreviations: BAL, bronchoalveolar lavage; TBB, transbronchial biopsy.

## BAL and TBB yields according to specific diagnosis

Of all samples, 247 samples were useful for diagnosis, 173 (70%) samples were obtained with TBB, and 161 (65.2%) samples were obtained with BAL; 92.3% (228) led to the identification of an infectious cause, while 13 (5.3%) corresponded to benign neoplasia and 6 (2.4%) corresponded to malignant neoplasia. The most frequent infection was fungal infection in 57.5% (131/228), followed by bacterial infection in 18.9% (43/228), mycobacterial infection in 16.2% (37/228), and viral infection in 7.5% (17/228). *P. jirovecii* was the most frequently identified pathogen in 91.6% (107), followed by *M. tuberculosis* complex in 93.8% (32) (Table 2).

BAL was a better tool for the identification of mycobacteria (94.6% vs 32.4%,  $P<0.001$ ) and viruses (70.6% vs 35.3%,  $P=0.001$ ) except CMV. Regarding the latter, TBB identified all cases of CMV infection, with only 1/6 being isolated through BAL. As for fungal infection, TBB performed better than BAL (87.0% vs 67.2%,  $P<0.001$ ). With respect to bacteria, there was no difference between both techniques, except *Escherichia coli* (Gram-negative Enterobacteriaceae) for which TBB was superior (82.4% vs 52.9%,  $P<0.001$ ) (Table 3). TBB was the only method that led to the diagnosis of neoplasia either benign or malignant (Table 4).

The overall concordance between TBB and BAL was nonsignificant ( $\kappa=0.213$ ,  $P<0.001$ ); however, it improved for the following diagnostic categories: fungal infections ( $\kappa=0.417$ ,  $P<0.001$ ), PJP ( $\kappa=0.583$ ,  $P<0.001$ ), and tuberculosis ( $\kappa=0.462$ ,  $P<0.001$ ) (Table 5).

## Coinfections

Positive isolates were obtained from 79.3% (157) procedures, and 35.0% (55) of them occurred as coinfections. The agents more frequently isolated from coinfections were *P. jirovecii* in 44/55 (80.0%) and *M. tuberculosis* complex in 19/54 (34.5%). In contrast, of all patients who had *P. jirovecii*, 41.1% (44/107) had a coinfection, and of all patients who had *M. tuberculosis* complex, 59.4% (19/32) had also coinfection. The following data were found to be nonsignificant regarding the development of infections with one or more organisms (coinfections) or the type of infectious agent: previous antibiotic treatment, length of treatment, and previous ART.

## PJP

Regarding PJP, BAL had a sensitivity of 71.9%, with a negative predictive value (NPV) of 75.2% and a diagnostic precision of 84.9%, while TBB for PJP diagnosis had a

**Table 2** Diagnostic yield according to the type of sample in HIV-infected patients with pneumonia

Type of sample according to diagnosis	TBB		BAL		Total		P*
	n	%	n	%	n	%	
Etiologic agent	154	67.5	161	70.6	228		
Fungal	114	87.0	88	67.2	131		<0.001
Mycobacteria	12	32.4	35	94.6	37		<0.001
Bacteria	22	51.2	26	60.5	43		0.189
Viruses	6	35.3	12	70.6	17		0.001
Benign diagnosis (other than infections)	13	100.0	0	0.0	13	5.3	
Malignancies	6	100.0	0	0.0	6	2.4	
Diagnostic yield according to origin							
Diagnostic yield of bronchoscopies	156	78.8	123	62.1	174	87.9	0.001
Total number of diagnoses reached from samples	173	70.0	161	65.2	247	100	0.001

Note: \*P-value for  $\chi^2$ .

Abbreviations: BAL, bronchoalveolar lavage; TBB, transbronchial biopsy.

**Table 3** Infectious etiologic agent identified in 157 procedures performed on HIV-infected patients with pneumonia according to the sample obtained

Diagnosis	TBB		BAL		Total	%	P*
	n	%	n	%			
Fungal							
<i>Pneumocystis jirovecii</i>	98	91.6	76	71.0	107	57.5	<0.001
Dimorphic fungi	10	58.8	11	64.7	17		<0.001
Yeasts	5	83.3	1	16.7	6		
Molds	3	100.0	0	0.0	3		
Subtotal	116	88.5	88	67.2	131		0.001
Mycobacteria							
<i>Mycobacterium tuberculosis</i>	12	37.5	30	93.8	32	16.2	<0.001
MAC	2	40.0	4	80.0	5		0.080
Subtotal	14	37.8	34	91.9	37		<0.001
Bacteria							
Gram-negative Enterobacteriaceae	14	82.4	9	52.9	18	18.9	<0.001
Gram-negative non-Enterobacteriaceae	2	14.3	12	85.7	14		
Gram-positive rods	0	0.0	1	100.0	1		
Gram-positive cocci	5	62.5	3	37.5	8		
Atypical bacteria	0	0.0	1	100.0	1		
Subtotal	21	48.8	26	60.5	43		<0.001
Viruses							
Respiratory viruses	0	0.0	11	100.0	11	7.5	
Cytomegalovirus	6	100.0	1	16.7	6		
Subtotal	6	35.3	12	70.6	17		
Total	154	67.5	161	70.6	228	100.0	

Note: \*P-value for  $\chi^2$ .

Abbreviations: BAL, bronchoalveolar lavage; MAC, *Mycobacterium avium* complex; TBB, transbronchial biopsy.

sensitivity of 89.7%, an NPV of 89.2%, and a diagnostic precision of 94.4%.

## Tuberculosis

The prevalence of tuberculosis in our population was 16.2% (32/198). Diagnosis was performed through samples obtained by culture in BAL in 93.8% (30/32), by GeneXpert in BAL in 53.1% (17/32), and by culture in TBB in 37.5%

(12/32). TBBs added the 6.3% (2) to the overall prevalence that would have not been obtained by BAL. The sensitivity of GeneXpert in BAL compared with culture in BAL, as the gold standard, was 56.7% (39.2–72.6), with a specificity of 100% (96.5–100), a positive predictive value of 100% (81.6–100), an NPV of 89.2% (82.3–93.6), a diagnostic precision of 90.5% (84.4–94.4), and Cohen's kappa concordance 0.67 (0.5132–0.8295,  $P<0.001$ ). When the sum

of tuberculosis diagnoses by culture and GeneXpert® by BAL and TBB culture was used as gold standard, sensitivity was 53.1% (35–70.5), with a specificity of 100% (97–99.9), a positive predictive value of 100% (77.1–99.5), an NPV of 91.2% (85.7–94.8), and a diagnostic precision of 92.0% (85.7–94.8) (Table 5).

## Yield of BAL and TBB according to tomographic imaging

We could retrieve tomographic studies from 155 (78.3%) patients. A better correlation was observed for TBB than for BAL in ground glass opacities (84.3% vs 66.1%,  $P=0.008$ ), consolidation (88.3% vs 63.6%,  $P=0.04$ ) or cysts (90.9% vs 68.2%,  $P=0.03$ ). These differences were significant.

## Complications

Safety was a crucial concern for the implementation of the BAL and TBB procedures. Complications occurred in 8.1% (16/198) of patients; in total, they accounted for 22 events. All cases were fully resolved, and no perioperative deaths occurred. The complications and their management for each

one were as follows: pneumothorax with chest tube placement (4.5%); desaturation with supplemental oxygen (3%); bronchospasm with bronchodilator nebulization (0.5%); moderate bleeding (2.5%), which was controlled with cold saline solution instillation, argon plasma cauterization balloon occlusion, and/or saline solution plus adrenaline instillation. Finally, patients who required intubation were 0.5% (Table 6).

## Discussion

Globally, microorganism isolation with all methods used was 87.9%, with TBB being superior to BAL (78.8% vs 62.1%,  $P=0.001$ ); these results are comparable to those from Cazzadori et al.<sup>9</sup> In their study, 79 HIV-infected patients with lung infiltrates were subjected to 84 bronchoscopies with a positive yield of 79.7%, being higher for TBB than for BAL (77.3% vs 47.6%,  $P<0.001$ ), and TBB increased the diagnostic yield of BAL in 32.1%. Salzman et al<sup>10</sup> also reported an additional 26% yield when TBB was obtained in 205 bronchoscopies performed in 182 HIV-infected patients. In general, both methods are useful in these patients. Regarding PJP, BAL can detect this infection in up to 90% of cases.<sup>11</sup> This figure can reach 100% when it is combined with TBB.<sup>12</sup>

In our population, 57% had CD4 counts <50 cells/mL and 85.5% had CD4 counts <200 cells/mL; at CD4 levels >400 cells/mL, patients are at risk of infection by relatively virulent organisms, such as bacteria and tuberculosis (TB). Lung cancer can also occur at this stage. This explains coinfections in HIV-infected patients, where etiologic agents were isolated in 79.3% of procedures and 34.4% had an additional coinfection, with *P. jirovecii* being the most frequent followed by *M. tuberculosis* complex. The most frequent coinfection was *P. jirovecii* with *M. tuberculosis* complex followed by *P. jirovecii* with *Histoplasma capsulatum*. With CD4 cell counts between 200 and 400 cells/mL, patients may experience recurrent infection, as well as lymphoma. Opportunistic infections and Kaposi's sarcoma are rare at CD4 levels

**Table 4** Noninfectious diagnoses according to sample type in HIV-infected patients with pneumonia

Noninfectious diagnoses	TBB		BAL		Total
	n	%	n	%	
Noninfectious benign diagnoses					
Histopathological pneumonia diagnosis, not culture proven	6	100.0	0	0.0	6
Granulomatous disease	5	100.0	1	20.0	5
Alveolar hemorrhage	3	100.0	0	0.0	3
Total	14	100.0	1	0.0	14
Malignancies					
Kaposi's sarcoma	3	100.0	0	0.0	3
B-cell lymphoma	2	100.0	0	0.0	2
Adenocarcinoma	1	100.0	0	0.0	1
Total	6	100.0	0	0.0	6

**Abbreviations:** BAL, bronchoalveolar lavage; TBB, transbronchial biopsy.

**Table 5** Kappa concordance index between TBB and BAL according to specific diagnoses in HIV-infected patients with pneumonia

Diagnosis	TBB		BAL		Total		Kappa index	P*
	n	%	n	%	n	%		
Bacterial infections	20	10.1	25	12.6	41	20.7	0.074	0.295
Viral infections	6	3.0	9	4.5	13	6.6	0.239	0.001
Fungal infections	102	51.5	84	42.4	122	61.6	0.417	<0.001
Malignancies	6	3.0	0	0.0	6	3.0	0	
Total	156	78.8	123	62.1	174	87.9	0.213	0.001
<i>Pneumocystis jirovecii</i>	96	48.5	77	38.9	107	54.0	0.583	<0.001
<i>Mycobacterium tuberculosis</i>	13	6.6	30	15.2	32	16.2	0.462	<0.001

**Note:** \*P-value for  $\chi^2$ .

**Abbreviations:** BAL, bronchoalveolar lavage; TBB, transbronchial biopsy.

**Table 6** Complications after transbronchial biopsy and bronchoalveolar lavage in HIV-infected patients with pneumonia

Patient	Pneumothorax, n (%)	Desaturation, n (%)	Moderate bleeding, n (%)	Bronchospasm, n (%)	Intubation, n (%)	Diagnosis
	9 (4.5%)	6 (3.0%)	5 (2.5%)	1 (0.5%)	1 (0.5%)	
1	0	0	1	0	0	<i>Pseudomonas aeruginosa</i>
2	0	0	0	1	0	<i>Pneumocystis jirovecii</i> and <i>Mycobacterium tuberculosis</i>
3	0	1	0	0	0	Without diagnosis
4	1	0	0	0	0	<i>Pneumocystis jirovecii</i> , enterovirus/ rhinovirus
5	1	0	0	0	0	<i>Pneumocystis jirovecii</i> and Kaposi's sarcoma
6	1	0	0	0	0	<i>Pneumocystis jirovecii</i>
7	0	0	1	0	0	<i>Pneumocystis jirovecii</i> and <i>M.</i> <i>tuberculosis</i>
8	1	1	0	0	0	<i>Pneumocystis jirovecii</i> , <i>M. tuberculosis</i> , and Follicular bronchiolitis
9	0	0	1	0	0	<i>Pneumocystis jirovecii</i> and <i>Streptococcus gordonii</i>
10	0	1	0	0	1	<i>M. tuberculosis</i>
11	1	1	1	0	0	<i>Pneumocystis jirovecii</i>
12	0	0	1	0	0	<i>Pneumocystis jirovecii</i>
13	1	1	0	0	0	<i>Pneumocystis jirovecii</i>
14	1	1	0	0	0	<i>Pneumocystis jirovecii</i> and enterovirus/rhinovirus
15	1	0	0	0	0	<i>Pneumocystis jirovecii</i> , <i>Escherichia coli</i> , and <i>Enterobacter cloacae</i>
16	1	0	0	0	0	<i>Pneumocystis jirovecii</i>

>200 cells/mL, and in fact, most PJP cases occur at CD4 cell counts <100 cells/mL, together with *Mycobacterium avium* complex (MAC), fungal infections, and CMV.<sup>13</sup> The population in the study by Cattamanchi et al<sup>14</sup> had a median CD4<sup>+</sup> T-lymphocyte count of 60 cells/mL (IQR 22–200 cells/mL), and 16% were receiving ART. TB prevalence by culture was 38%, but it was positive in only 5.3% in BAL culture. The incidence of bacterial pneumonia increases starting from CD4 cell counts <200 cells/mL in HIV-infected patients.<sup>1,15</sup>

In our population with known history of antibiotic use prior to bronchoscopy or antiretroviral treatment, 92.8% took antibiotics and 36.6% took ART; no statistically significant differences were found between patients with previous antibiotic use, the days with previous antibiotic, or with previous ART with the identification of etiologic agent, the presence of coinfections, or the types of etiologic agents identified. Bronchoscopic procedures are useful even after the initiation of empirical treatment if treatment duration has not exceeded 1 or 2 weeks.<sup>11</sup>

Regarding BAL yield for the diagnosis of PJP, Golden et al<sup>16</sup> reported a 97% sensitivity, although considering their sample size, a 75% NPV is obtained (95% CI 30.1–95.4), and therefore, consideration must be given to their conclusions, in

which they suggest the replacement of TBB by BAL. In fact, they did not directly study the role of TBB. Our results, with the sensitivities of 71.9% (95% CI 62.8–79.6) for BAL and 89.7% (95% CI 82.5–84.2) for TBB and  $\kappa=0.583$  for both methods, support the opposite. The latter is similar to the results obtained by Broaddus et al,<sup>17</sup> who reported an 86% yield for BAL and 87% for TBB. When both procedures were performed in the same study, the combined yield for all lung infections was 96%. In contrast, Coleman et al<sup>18</sup> reported the global sensitivities of 79 and 55% for the diagnosis of PJP by TBB and BAL, respectively.

In other series, the additive yield of TBB seems to be more important when other infections, besides PJP, are present. In this setting, Batungwanayo et al<sup>19</sup> reported the diagnostic yields of 82% and 26%, respectively, for TBB and BAL, but this reflects the wide spectrum of lung complications in African populations, where PJP is rare, but nonspecific interstitial pneumonia, TB, and *Cryptococcal pneumonia* were the most common diagnoses. In a retrospective analysis of 205 bronchoscopies in 182 patients, Salzman et al<sup>20</sup> demonstrated that 26% of diagnoses were exclusively obtained with TBB, which was also the only source for the diagnosis of noninfectious

conditions in over half of those cases (54%). In other series of HIV-infected patients, the global yield of TBB is superior to that of BAL (80% vs 57.1%), but sample sizes are small.<sup>21</sup>

Diagnoses of granulomatous inflammation were classified as benign, as no microbiological confirmation of infection was obtained. Nonetheless, in some studies, this finding is regarded as either tuberculosis or histoplasmosis, which can be overestimated.<sup>20</sup> Miro et al<sup>22</sup> concluded that in tuberculosis-infected patients, neither TBB nor bronchial brushings increased the diagnostic yield. In contrast to their study, our study included not only TB but also other diagnoses, which were demonstrated from TBB and BAL sampling.

The prevalence of tuberculosis in our study was higher than that previously reported in other series, even when a low sensitivity of BAL GeneXpert was observed and even though sputum production in these patients was negligible.<sup>23</sup> This was overcome by the combination of BAL culture and BAL GeneXpert, which we did to obtain optimal samples. In contrast, TBB added some TB cases, which were not isolated by BAL. Based on this assertion, it is necessary to consider TBB samples to be routinely sent to mycobacterial culture.<sup>24,25</sup>

We found lower frequencies of CMV in BAL and of coinfections in the setting of PJP, as observed in other series. However, some of these did not look for this agent by TBB, in contrast to our study, in which diagnosis was supported with TBB findings in all six cases, with only one case showing CMV in BAL. All CMV cases were, in fact, coinfecting with other pathogens (*M. tuberculosis*, *Haemophilus influenzae*, *Enterococcus faecalis*, *Candida albicans*, enterovirus, and parainfluenza type 3 virus), and five of the six cases also had PJP.<sup>11,26–30</sup>

Regarding specific diagnosis in relation to the sampling method, Shafiek et al<sup>31</sup> found a 93% concordance of BAL with laser confocal endomicroscopy in 32 patients, but they did not compare this with TBB. Stover et al<sup>11</sup> took as gold standard the samples obtained via bronchoscopy from BAL, TBB, cytology, BAL and/or postmortem. They found that 65% of patients had specific germ isolation. Specific figures for each diagnosis were as follows: 94% for PJP, 67% for CMV, 62% for MAC, and 0% for SK. For PJP, the highest yield was obtained when combining TBB and BAL. As for PJP, TBB had an 88% yield with an 85% yield for BAL, but the combination of both methods led to the best yield. Our figures also support that performance of both techniques in combination yields better results. Specifically, 54% of the patients we studied had PJP. The differences found by using each method, BAL 51 vs TBB 91.6%,  $\kappa=0.583$  ( $P<0.001$ ), show that both sampling techniques are complementary.

Cancer prevalence in our population was 2.4%, and the diagnoses were demonstrated solely by TBB. It is important to remember that HIV causes a 3.5-fold increase in the risk of lung cancer and that it also occurs earlier, and its mean survival is only 3–4 weeks.<sup>6,13,32</sup>

We found alveolar hemorrhage (AH) in 4.5% of patients, diagnosed solely by TBB. This finding occurred in association with various infections (PJP, *M. tuberculosis*, *H. influenzae*, *Coccidioides immitis*, MAC, and enterovirus). This was lower than that reported in the study by Vincent et al,<sup>33</sup> who found a 32% prevalence of AH. In their article, associations of AH with other conditions (CMV and Kaposi's sarcoma) were also observed. Regarding granulomatous inflammation and pneumonia without isolation of specific pathogens, these were suggested by the histopathological findings of TBB.

Among benign diagnoses, AH had a 4.5% (nine patients) prevalence in our study and the diagnosis was obtained solely by TBBs; however, since six of these patients had some other diagnosis, at the end, the specific diagnosis was considered and the AH diagnosis was given to only three of the nine patients. Each six patients had an infection, including PJP, *M. tuberculosis*, *H. influenzae*, *C. immitis*, MAC, and enterovirus. These results contrast with those reported by Vincent et al<sup>33</sup> in their study of HIV-infected patients with pulmonary symptoms, in which the prevalence of AH was 32% but only in BAL samples, where CMV infection (OR 9.8 [95% CI 1–91],  $P=0.05$ ) and pulmonary Kaposi's sarcoma (OR 5.3 [95% CI 1.8–16.7],  $P=0.003$ ) were among the main associated factors. Regarding pneumonia without isolation of the etiologic agent and granulomatous inflammation, the diagnoses were obtained by TBB through histopathological observation.

Finally, our complication figures were comparable to others, with pneumothorax in 4.5% and mild-to-moderate bleeding in 2.5%.<sup>10,11,18</sup>

We acknowledge the following limitations, which could have increased the diagnostic yield of each sample (BAL and TBB): lack of a larger panel for viral diagnosis via PCR and lack of specific antigen search of other microorganisms, including TB. This study has internal validity, but the external one will depend on the experience of the center in the care of patients with HIV and pneumonia and in pulmonary interventionism.

## Conclusion

Our results show that the diagnosis through BAL and TBB samples is discrepant; so the simultaneous study of both samples would mean a greater diagnostic opportunity, their obtainment is safe, and they are very useful techniques to

specifically diagnose infections and malignancies in HIV-infected patients with pneumonia.

## Disclosure

The authors report no conflicts of interest in this work.

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